

EXHIBIT E

ORIGINAL ARTICLE

The IUGA/ICS classification of synthetic mesh complications in female pelvic floor reconstructive surgery: a multicenter study

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Abstract

Introduction and hypothesis The objective was to report patterns of sling and transvaginal mesh-related complications using the IUGA/ICS classification of prosthesis-related complications.

Methods This was a retrospective chart review of all patients who underwent surgical removal of sling, transvaginal mesh, and sacrocolpopexy for mesh-related complications from 2011 to 2013 at three tertiary referral centers. The International Urogynecological Association (IUGA)/International Continence Society (ICS) classification system was utilized.

Results We identified 445 patients with mesh complications. 506 pieces of synthetic mesh were removed, and 587 prostheses-related complications were classified. 3.7 % of patients had viscus organ penetration or vaginal exposure as their presenting chief complaint and 59.7 % were classified as not having any vaginal epithelial separation or category 1. The most common category was spontaneous pain (18c; 32.5 %) followed by dyspareunia (18c; 14.7 %). The sling group was 20 % more likely to have pain compared with the pelvic organ prolapse (POP) mesh group (OR 1.2, 95 % CI 0.8–1.6). The most commonly affected site (S2) was away

from the suture line (49 %). Compared with the sling group, the POP group had a higher rate of mesh exposure, which mostly occurred at the suture line area. The majority of patients presented with mesh-related complications more than 1 year post-insertion (T4; average 3.68 ± 2.47 years).

Conclusion Surgeons should be aware that patients with vaginal mesh complications routinely exhibit complications more than 1 year after the implantation with pain as the most common presenting symptom.

Keyword Mesh complication · IUGA/ICS classification · Sling complication · Transvaginal mesh · Mesh removal · Mesh complication classification

Introduction

The use of surgical mesh for the repair of pelvic organ prolapse (POP) and stress urinary incontinence (SUI) has increased substantially over the last 15 years with the advent of mesh kits for slings and transvaginal mesh (TVM) kits for POP. The popularity of these mesh kits surged because surgeons believed they produced higher cure rates and were easier to perform [1–4]. However, as the use of synthetic mesh increased, so did reports of complications. These two points have called into question the true overall risks of mesh use in female pelvic surgery. Owing to the elevated occurrence of reported mesh complications, the US Food and Drug Administration (FDA) issued a Public Health Notification in 2008 concerning the serious complications of surgical mesh placed via the vagina to treat POP and SUI. In 2011, the FDA issued an UPDATE based on a recent review of the medical literature, and additional FDA-reported complications. The report suggests that surgical mesh for the transvaginal repair of POP might be an area of serious concern [5]. The most commonly

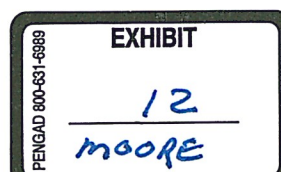
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reported complications included mesh exposure through the vaginal epithelium, erosion into the visceral organs, infection, pain, dyspareunia, urinary problems, fistula formation, bladder perforation, and the recurrence of POP/SUI [2, 6, 7]. These complications have been reported after the use of not only transvaginal mesh kits and mesh tape slings, but also after abdominal mesh surgery, such as sacrocolpopexy and hysteropexy. Risk factors reported to be associated with complications included: operative technique, surgeon experience, previous prolapse repair, concomitant hysterectomy, inverted T colpotomy during concomitant hysterectomy, total vaginal mesh repair, mesh properties, younger age at the time of surgery, sexual activity, and smoking [8, 9].

Ultimately, the FDA ordered post-market surveillance studies (i.e., 522 studies) for transvaginal mesh surgical repair of POP in an attempt to scientifically support the continued marketing and use of these products. The FDA also stated that physicians should be properly trained to perform TVM kit placement and patients informed of the risks of mesh and about alternative treatment options [10]. In response to the issue, the International Urogynecology Association/International Continence Society (IUGA/ICS) created a uniform classification system to systematically report mesh complications in a standardized manner [11], whether reporting on transvaginal or abdominal approaches. In addition, the system was designed to be a common language for providers to communicate consistently regarding complications and to be a universal system for collecting data on mesh-related complications. The objective of this study was to report the patterns of sling and POP mesh-related complications using the IUGA/ICS classification of prosthesis-related complications at three centers, for women who had undergone pelvic floor reconstructive surgery with mesh.

Materials and methods

This was a retrospective chart review of all female patients who underwent surgical removal of sub-urethral mesh slings, transvaginal synthetic mesh (TVM), and sacrocolpopexy (SC) for mesh-related complications from January 2011 to December 2013 at three tertiary referral centers in the south east of the USA. The centers included were the International Urogynecology Associates (IUA) of Atlanta and Beverly Hills, Emory University (EU), and Cleveland Clinic Florida (CCF). The IUGA/ICS classification system for prostheses complications was used to report complications.

After IRB approval, the database was queried to identify potential subjects. All patients who presented to the three institutions with complaints related to mesh placement and subsequently underwent surgery to remove the mesh were included in the analysis. The surgical revision and/or removal included cutting of the mesh, partial removal of the synthetic

mesh, total vaginal mesh removal, groin mesh removal, and laparoscopic retroperitoneal/intra-abdominal mesh removal. The patients' complaints were determined at the first visit. Physical examinations including a pelvic examination were completed. Every complaint was categorized by the examining physician as a CTSP code (Category, Time, Site, and Pain) following the ICS/IUGA Complication Classification Code guidelines (Table 1).

Data were analyzed by using Chi-squared test for categorical data, and Student's *t* test and the Wilcoxon rank sum test for continuous data. The measure of effect was determined by logistic regression analysis.

Results

We identified 445 patients with mesh complications who subsequently underwent mesh revision/removal transvaginally, via groin dissection and/or via a laparoscopic approach. A number of patients presented with several complaints. Of the complications identified, 178 (40 %) were from transvaginal mesh inserted for POP, 373 (83.8 %) from a sub-urethral sling, and 38 (8.5 %) from sacrocolpopexy. The mean age was 53.8 ± 11.2 years and parity 2.5 ± 1.2 . Most patients were Caucasian (82.0 %), postmenopausal (72.8 %), sexually active (52.1 %), and insured (76.4 %). Eighty-three percent had undergone a previous hysterectomy and 92.6 % had previously been seen by a different physician(s). Twenty-five percent were current smokers. Twenty-eight percent had undergone a previous mesh revision or removal.

The most common chief complaint amongst patients was pain (68.6 %) with or without intercourse. Only 3.7 % of patients had viscus organ erosion or vaginal exposure as their chief presenting complaint. Seventy-five percent (335 out of 445) of these patients had their mesh removed at IUA, 14.8 % (66 out of 445) at CCF, and 9.9 % (44 out of 345) at EU. IUA had the most diverse types of approaches to mesh removal including: 91.9 % (308 out of 335) transvaginal, 24.8 % (83 out of 335) laparoscopic, and 8 % (27 out of 335) by groin dissection. One hundred percent of EU (44 out of 44) and CCF (66 out of 66) patients respectively had their mesh removed transvaginally and 5 % (2 out of 44) of EU patients had mesh removed via groin dissection. Mesh was removed by neither EU nor CCF via the laparoscopic approach.

According to the IUGA/ICS classification, 59.7 % were classified as having no vaginal epithelial separation (category 1). The most common category was spontaneous pain (without activity, examination or intercourse, 1Be; 32.5 %) followed by dyspareunia (1Bc; 14.7 %). Most patients presented with mesh-related complications over a year after insertion (T4). The sling group was 20 % more likely to have pain compared with the POP group (OR 1.2, 95 % CI 0.8–1.6). The most commonly affected site (S2) was away from the

Table 1 International Urogynecological Association/International Continence Society (IUGA/ICS) classification of complications related directly to the insertion of a prosthesis in female pelvic reconstructive surgery (506 mesh removed, 587 complications classified), *n* (%)

Classification	Overall (<i>n</i> = 587)	Comparison of mesh sling for SUI with mesh for POP		
		SUI (<i>n</i> = 337)	POP (<i>n</i> = 250)	<i>p</i> value
Category				
1. Vaginal: no epithelial separation	349 (59.66)	227 (67.96)	121 (48.40)	<0.001
2. Vaginal: smaller ≤1 cm exposure	81 (13.82)	37 (11.08)	44 (17.60)	0.024
3. Vaginal: larger >1 cm exposure, or any extrusion	87 (14.86)	23 (6.89)	64 (25.60)	<0.001
4. Urinary tract: compromise or perforation including prosthesis (graft) perforation and fistula	27 (4.61)	19 (5.69)	8 (3.20)	0.157
5. Rectal or bowel: compromise or perforation including prosthesis (graft) perforation and fistula	6 (1.03)	2 (0.60)	4 (1.60)	0.235
6. Skin or musculoskeletal: complications including discharge, pain, lump, or sinus tract formation	34 (5.81)	25 (7.49)	9 (3.60)	0.047
7. Patient: compromise including hematoma or systemic compromise	1 (0.17)	1 (0.30)	0 (0)	0.387
Time (clinically diagnosed)				
T1: Intraoperative to 48 h	1 (0.17)	1 (0.30)	0 (0)	1.000*
T2: 48 h to 2 months	14 (2.39)	8 (2.40)	6 (2.40)	0.997
T3: 2 months to 12 months	61 (10.43)	31 (9.28)	30 (12.00)	0.288
T4: over 12 months	509 (87.01)	294 (88.02)	214 (85.60)	0.389
Site				
S1: vaginal: area of suture line	140 (23.97)	50 (14.97)	90 (36.14)	<0.001
S2: vaginal: away from suture line	286 (48.97)	176 (52.69)	109 (43.78)	0.033
S3: trocar passage	34 (5.82)	20 (5.99)	14 (5.62)	0.852
S4: other skin or musculoskeletal site	82 (14.04)	60 (17.96)	22 (8.84)	0.002
S5: intra-abdominal	42 (7.19)	28 (8.38)	14 (5.62)	0.202
Pain				
U: unspecified	0 (0)	0 (0)	0 (0)	N/A
a: asymptomatic or no pain	136 (23.45)	70 (21.21)	65 (26.21)	0.160
b: provoked pain only	18 (3.10)	11 (3.33)	7 (2.82)	0.727
c: pain during sexual intercourse	128 (22.07)	67 (20.30)	61 (24.60)	0.219
d: pain during physical activities	30 (5.17)	22 (6.67)	8 (3.23)	0.652
e: spontaneous pain	268 (46.21)	160 (48.48)	107 (43.15)	0.203

*Fisher's exact test

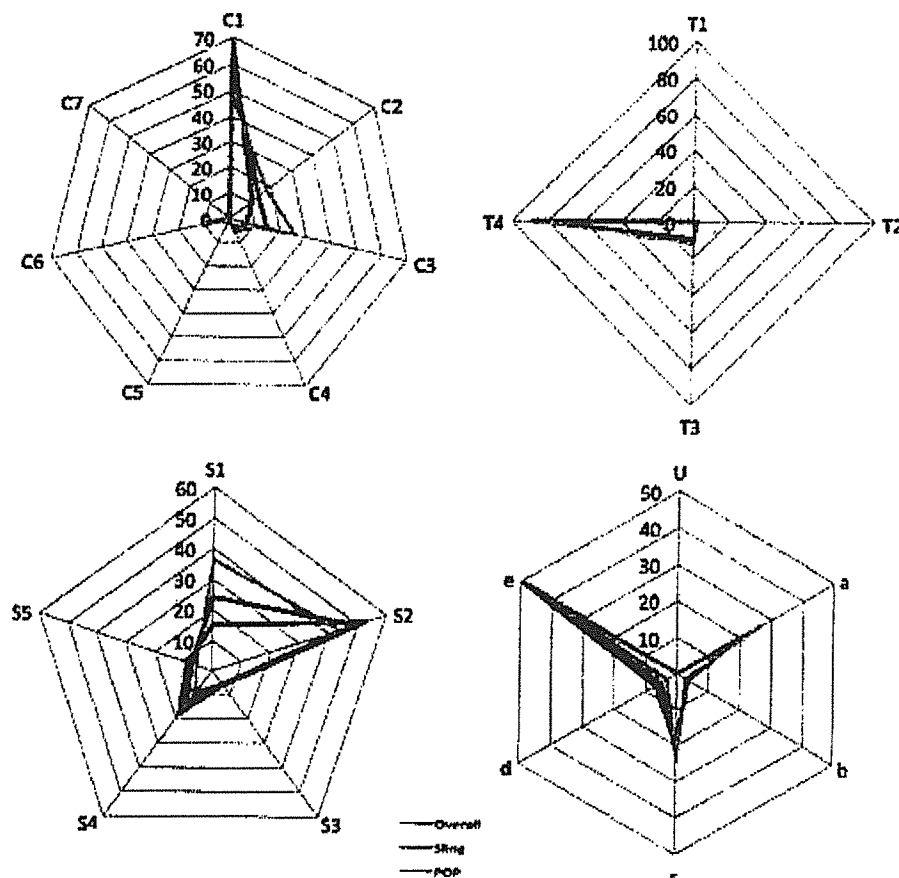
suture line (49 %; Fig. 1). Compared with the sling group, the mesh for POP group had higher rates of exposure (less than 1 cm exposure: 17.6 % vs 11.1 %, $p = 0.024$, more than 1 cm exposure: 25.6 % vs 6.9 %, $p < 0.001$) and they were more likely to occur at the area of the suture line (36.1 % vs 15.0 %, $p < 0.001$). However, the sling group had more complications in category 1 vaginal: no epithelial separation (68.0 % vs 48.4 %, $p < 0.001$) and category 6: skin and musculoskeletal (7.5 % vs 3.6 %, $p = 0.047$). The average interval before a presenting complication was 3.68 ± 2.47 years after mesh insertion (median 3 years, range 0–18 years). There were no differences in the timing of the presentation of the complication among TVM, sling, and SC ($p = 0.133$ Table 1). Regarding patterns of classification, both mesh slings and mesh for POP had similar complication patterns in terms of category, time, site, and pain (Fig. 1). In a subgroup analysis of sling

types, the interval from insertion to presenting complications among the retropubic sling (RP) group was statistically longer than for the transobturator sling (TOT) group (4.26 ± 3.22 vs 3.69 ± 2.41 years, p value 0.002) and the single-incision sling (SIS) group (4.26 ± 3.22 vs 2.72 ± 1.64 years, $p < 0.001$). SIS had the shortest interval before a complication presented compared with TVT (2.72 ± 1.64 vs 4.26 ± 3.22 years, $p < 0.001$) and TOT (2.72 ± 1.64 vs 3.69 ± 2.41 years, $p = 0.007$; Table 2).

Discussion

A Cochrane review of the surgical management of female POP found that transvaginal mesh exposure accounted for an 11 % complication rate; however, this review did not

Fig. 1 Radar plot of IUGA/ICS classification of complications related directly to the insertion of a prosthesis in female pelvic reconstructive surgery (%). *C1: vaginal; no epithelial separation; C2: vaginal; smaller ≤ 1 cm exposure; C3: vaginal; larger > 1 cm exposure, or any extrusion; C4: urinary tract: compromise or perforation including prosthesis (graft) perforation and fistula; C5: rectal or bowel: compromise or perforation including prosthesis (graft) perforation and fistula; C6: skin or musculoskeletal; complications including discharge, pain, lump, or sinus tract formation; C7: patient: compromise including hematoma or systemic compromise. S1: vaginal: area of the suture line; S2: vaginal: away from the suture line; S3: trocar passage; S4: other skin or musculoskeletal site; S5: intra-abdominal, U: unspecified; a: asymptomatic or no pain; b: provoked pain only; c: pain during sexual intercourse; d: pain during physical activities; e: spontaneous pain



mention other complication rates, especially those that were related to pain [12]. In our experience, when a woman presents with dissatisfaction following a vaginal mesh procedure, her chief complaint is not always an objective finding such as an exposure, but instead it is a subjective complaint such as pain. Unger et al. reported that presenting symptoms of

mesh-related complications were mesh exposure (48 %), pelvic pain (38 %), and dyspareunia (32 %) [13]. Firoozi et al. reported that the most common indications for mesh removal included vaginal/pelvic pain (39 %) and dyspareunia (39 %) [14]. Their cohort had no thigh or groin pain related to the trocar-guided arms of the synthetic mesh; thus, they removed only the vaginal portion of the mesh via a transvaginal approach. From our cohort, we also found that pain was the primary indication for mesh removal and not mesh exposure. In an attempt to objectively identify the source of a woman's pain we found that it is beneficial to focus the examination away from the suture line (i.e., paraurethral or paravaginally) and not necessarily suburethral or at the central body of the mesh. In many instances we found that a patient did not have pain suburethral or in the central portion of the body of the mesh; however, they had significant pain lateral to the urethra or where the arms of the body of the mesh were anchored laterally. The point of mesh anchoring at the muscles and fascia such as the obturator internus, levator ani, and coccygeal muscle or fascia is often the point of maximum pain on examination. This pain is thought to be due to the scarring and contraction of the mesh that in turn pulls on the

Table 2 Interval between mesh insertion and removal (years)

	Mean (SD)	Median (range)	p value
Total (N = 497)	3.68 (2.47)	3.0 (0-18)	0.133*
Sling (n = 311)	3.78 (2.72)	3 (0-18)	
TVM (n = 194)	3.44 (2.00)	3 (0-10)	
SC (n = 29)	4.35 (2.42)	4 (1-10)	
Sling type			
RP (n = 109)	4.26 (3.22)	4 (0-18)	0.006*
TOT (n = 134)	3.69 (2.41)	3 (0-9)	
SIS (n = 39)	2.72 (1.64)	3 (0-7)	

*ANOVA

TVM transvaginal synthetic mesh, SC sacrocolpopexy, RP retropubic sling, TOT transobturator sling, SIS single-incision sling

nerve-laden muscles, thus creating pain. Failure to objectively reproduce the pain on examination may result in delayed diagnosis and treatment, or the suffering patients may even be denied treatment.

In our study, patients with sling complications suffering only vaginal pain (and not abdominal/suprapubic pain or groin pain) underwent a vaginal-only approach to removal of the sling. Patients also suffering from significant groin pain underwent groin dissection to remove the TOT sling mesh from the groin on the affected side. Patients suffering from vaginal and abdominal/suprapubic pain underwent both a vaginal and laparoscopic approach to remove the suburethral portion of the sling in addition to the retropubic arms of the sling from the pubocervical fascia to the abdominal wall.

All three study centers are sites for mesh complication referrals. The largest percentage of patients in this study came from the IUA site and this is most likely attributed to the Center's informative website and Internet optimization. We can also speculate that the reason why the IUA site has the highest percentage of laparoscopic and groin approaches to mesh removals is because the surgeons at IUA specifically attempt to remove the maximum amount of mesh, if the patient has pain symptoms specific to the point of mesh attachment or the mesh pathway. Additionally, the IUA surgeons saw statistically more patients than either of the other centers. Therefore, they would be presented with more patients with these less common complications. Patients with confirmed apical vaginal pain following sacrocolpopexy, lower abdominal wall pain post-RP slings or inguinal pain after TOT slings were subjected to the most aggressive operations, which included either a laparoscopic or inguinal approach to attain maximum mesh removal.

Previous publications reported that the duration between mesh implantation and mesh removal/revision was 1.3 years [11] and 10 months [14]. Marcus-Braun and von Theobald reported a case series of mesh removal during a 5-year period and found that majority of mesh-related complications occurred more than 2 years after mesh placement [15]. Based on these results surgeons should be aware that patients with mesh complications are routinely presenting more than 1 year after the initial surgery. Our data show that the average time at which a diagnosis of mesh complications is made in patients undergoing surgery for vaginal prolapse or stress urinary incontinence was greater than 3.5 years.

Our study implies that mesh-related complications could present in the long term, or greater than 1 year after implantation. This might be due to patients being previously misdiagnosed, as more than 90 % of these patients had been examined by other physicians before being seen at one of the three centers. Early diagnosis and surgical treatment of mesh complications is essential in reducing chronic pain due to nerve entrapment secondary to fibrosis and myofascial contraction, and/or the up-regulation of the central nervous system.

The strength of our study relies on the large number of patients that make up the cohort of cases of mesh-related complications and the fact that the data were gathered from three tertiary urogynecological referral centers with diverse patient populations. Additionally, all complications were uniformly classified utilizing the standard IUGA/ICS classification system. The impact of this study is limited by its retrospective and descriptive nature. In addition, this cohort may not represent the general population because it consisted of complicated and often recurrent cases. Other limitations of this study include the lack of outcomes after mesh revision/removal, including the possible improvement of symptoms, quality of life, and sexual function.

Conclusion

Based on the results of our study, surgeons should be aware that patients with mesh are routinely presenting with complications more than 1 year after the implantation surgery. Surgeons should note that while vaginal mesh exposure is a common complication of slings and POP mesh, it is more common in the latter and pain is generally the most common overall complication requiring intervention. In the majority of cases, the patient's chief complaint is not an objective finding (i.e., exposure), but more commonly it is a subjective complaint such as pain. In patients presenting with pain following mesh placement, we found that it may be beneficial for the examining physician to focus the examination away from the suture line (i.e., paraurethral or paravaginally). Failure to do so could result in a misdiagnosis, delaying necessary treatment and subjecting the patient to prolonged or unnecessary suffering.

Compliance with ethical standards

Conflicts of interest None.

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